

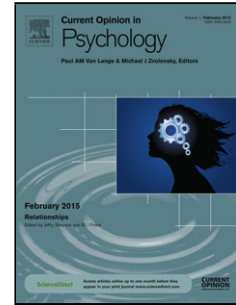
Accepted Manuscript

Title: Meditation, Stress Processes, and Telomere Biology

Authors: Quinn A Conklin, Alexandra D Crosswell, Clifford D Saron, Elissa S Epel

PII: S2352-250X(18)30200-8
DOI: <https://doi.org/10.1016/j.copsyc.2018.11.009>
Reference: COPSYC 737

To appear in:



Please cite this article as: Conklin QA, Crosswell AD, Saron CD, Epel ES, Meditation, Stress Processes, and Telomere Biology, *Current Opinion in Psychology* (2018), <https://doi.org/10.1016/j.copsyc.2018.11.009>

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Meditation, Stress Processes, and Telomere Biology

Quinn A. Conklin^{1*}, Alexandra D. Crosswell², Clifford D. Saron¹, and Elissa S. Epel^{2*}

1) University of California, Davis

2) University of California, San Francisco

*Corresponding authors:

Quinn A. Conklin (qconklin@ucdavis.edu) & Elissa S. Epel (Elissa.Epel@ucsf.edu)

Abstract

Both theoretical and empirical work support the notion that meditation training can improve telomere regulation, which may ultimately contribute to healthy aging. Yet, the psychological and biological mechanisms underlying these changes remain underspecified, as do the contexts and boundary conditions in which these changes occur. Here we summarize studies investigating the effects of various meditation-based interventions on telomere biology, making suggestions for future research. We then propose a model describing how meditation training

may impact acute and habitual stress responses as pathways to improved cell aging.

Telomeres are DNA-protein complexes that cap and protect eukaryotic chromosomes. These dynamic structures are regulated by an intricate system of proteins and other molecular components, including telomerase—an enzyme capable of elongating telomeres. When telomeres become too short, critical cellular events occur, including cell death or states of prolonged senescence and inflammatory output. As such, **telomere length (TL)** serves as a reliable indicator of many age-related diseases (e.g., dementia and heart disease [1]). Studies of genetics show that telomere biology plays a small but causal role in disease processes: for example, genetic loading for short TL predicts degenerative diseases such as cardiovascular disease, whereas genetic variation for longer telomeres predicts propensity for certain cancers, including glioma [2].

Telomeres generally shorten slowly across the lifespan. There is, however, some degree of malleability to this as telomeres tend to shorten more quickly in individuals exposed to long-term psychosocial adversity [3], but appear to stabilize or possibly lengthen in individuals engaged in positive lifestyle interventions (e.g., [4]). Meditation training is one such intervention that seems to beneficially affect telomere biology. In a previous theoretical model, we explored the impact of mindfulness meditation on TL [5]. In the decade since this model was published, a small body of research has emerged addressing the relationship between meditation practice and telomere-related outcomes (telomere length, telomerase activity, or telomere-related gene expression). Here, we review this empirical work and offer an updated model, depicted in **Figure 1**, which illustrates how various aspects of meditation training may impact telomeric regulation by influencing acute and habitual stress processes.

What we know so far:

A total of 19 studies have examined telomere biology in relation to meditation [6–24]. These studies vary in quality, though many constitute promising pilot studies that warrant replication and extension. Two cross-sectional studies found longer telomeres in experienced meditators compared to meditation-naïve controls ($n=20$ [7*]; $n=13$ [6], in women only). The remaining 17 studies examined telomere-related outcomes in relation to interventions involving or emphasizing meditation practice (**Table 1**). Of the eleven studies measuring **telomerase activity (TA)**, nine found intervention-related increases [9,10,18–24] or higher TA in the treatment group following intervention [17], while two found no significant changes in TA [8*,24]. By contrast, just two of the nine studies measuring TL—which involved interventions of relatively high intensity or duration—showed increased TL in the treatment group [8*,23]. The remaining seven studies found no significant change in TL [9–15].

Only four studies have assessed TA and TL concurrently, each of which reported significant intervention-related changes in one measure but not the other [8*–10,24]. These findings suggest that TA and TL have different kinetics and fluctuate on different time scales, consistent with the observation that TA and TL are generally uncorrelated in cross-sectional studies [25]. We hypothesize that meditation training promotes phasic increases in TA, which eventually lead to longer telomeres, though the duration of training needed to elicit these effects is unknown. Initial evidence suggests that these changes can happen rapidly: intensive retreat studies of experienced meditators have shown modest increases in TA in as little as one week [22*] and increases in TL in as little as three weeks [8*]. Because TA and TL were only assessed at the end of these interventions, the longevity of these effects is unknown.

It is largely assumed that meditation training influences telomere biology by reducing

psychological stress, though only a few studies have assessed whether stress-related processes actually mediate these relationships. Intervention-related increases in TA have been linked to improvements in quality of life [19], fewer intrusive thoughts [23], and reductions in anxiety, chronic stress, and basal cortisol [18]—though these associations have not been observed in all cases [9,14]. Another study found that increases in perceived control and purpose in life, and decreases in neuroticism, were associated with higher levels of TA following an intensive retreat [17]. More direct tests of stress-related psychological and biological mediators are needed to better understand these relationships over time.

Although the available evidence suggests that meditation training can improve telomere maintenance, it is unclear how and under what conditions these effects are achieved, and how long they persist. Because telomere regulation is dynamic and involves complex temporal features that are not yet fully understood, future studies should include more frequent measurements using gold standard methods [26**,27**]. As telomere biology varies by cell type, it will be informative for studies to assess TL in tissues with stable cell type distributions (e.g., buccal cells), in addition to more commonly used blood samples, which include a mix of shifting immune cell types (see Lin et al. [27**] for a discussion of the pros and cons of measuring TL in different sample types and with various assay methods). Finally, to gain the clearest mechanistic understanding, studies should measure psychological and physiological stress processes alongside multiple indicators of telomere biology and other biomarkers of aging.

Stress processes and their relation to telomere biology

The **acute stress response** traditionally refers to a range of cognitive, affective, behavioral, and physiological reactions to discrete stressors [28*], which are shaped by cognitive biases and basal physiological states. This multi-system response can involve **anticipatory**

arousal before a stressful event, **peak reactivity** during the event, and **recovery to baseline** following the event. Maladaptive forms of this acute stress response may lead to alterations in telomere regulation. For example, exaggerated autonomic reactivity has been associated with lower immune cell TA [29], and higher cortisol reactivity to stressors has been associated with shorter immune cell telomeres [30*] (but not buccal cell TL [31]). **Perseverative cognitions**, such as worry and rumination, can exacerbate profiles of heightened physiological reactivity and delayed recovery [32] and may serve as internal stressors in and of themselves. Importantly, shorter telomeres have also been linked to perseverative cognitions, including negative mind wandering [33] and greater anticipatory threat appraisals to an acute stressor [34].

Acute stress reactivity profiles are influenced by **allostatic states**, including basal levels of autonomic and neuroendocrine activity, metabolic hormones, and inflammation. Chronic exposure and prolonged reactivity to stressors can contribute to dysregulated allostatic states, with deleterious health consequences (e.g. [35]). Telomere regulation appears to be implicated in this relationship, as shorter telomeres and lower telomerase levels have been associated with lower vagal tone, and higher basal levels of cortisol, inflammation, and oxidative stress [3].

The acute stress response is activated by perceptions of threat to the physical or social self [36], yet these perceptions vary between people and between physical, social, and cultural contexts. **Cognitive biases** are the habitual mental filters that influence one's interpretations of the world, including mental representations of the self and others, and perceptions of one's environment. These cognitive biases are shaped by life experience. For example, having a history of early life adversity can lead one to anticipate negative events and to interpret neutral stimuli as negative (e.g. [37]). Cognitive biases that prime individuals to be hypervigilant to their environment—due to real or perceived threats—can lead to heightened allostatic states. It may be

that regularly feeling unsafe indirectly signals to cellular mediators that it is more important to sustain heightened biological stress arousal (i.e., to be on alert for threats) than to put energy towards cellular restoration. Along these lines, personality traits such as pessimism, neuroticism, and hostility have been linked to prolonged stress reactivity and shorter telomeres [38], suggesting that one's habitual interpretations of the world contribute to the relationship between stress exposure and telomere regulation.

Initial evidence suggests that various forms of meditation training can beneficially affect allostatic states (e.g., immune system functioning [39]) and the anticipatory [40], reactivity (e.g., [41]), and recovery [42] phases of the acute stress response. Yet these findings are inconsistent (for a review of cortisol studies, see [43]). Meditation interventions can vary significantly in the practices they emphasize, their pedagogical frameworks, and in their training environments—all of which may influence stress processes. Similarly, some practices may be more appropriate for particular individuals depending on the types of maladaptive stress responses they are most prone to (e.g., greater anticipatory threat or prolonged recovery). Accounting for these variables will facilitate more direct and nuanced hypothesis testing regarding the effects of meditation training on stress processes and outcomes.

Effects of meditation training on stress processes

Meditation practices represent a class of mental training techniques intended to regulate a range of psychological processes—particularly those having to do with perceptions of reality and the self [44**,45]. As such, we expect these techniques to target the cognitive biases that shape acute stress appraisals and responses, as well as the perseverative cognitions that prolong stress reactivity. In this way, continued meditation training should support experiential learning and self-understanding that lead to lasting improvements in health.

Meditation techniques can be usefully categorized according to the cognitive mechanisms they are believed to target. One contemporary classification system posits three families of practice: attentional, deconstructive, and constructive [44**]. The attentional family comprises practices used to train the self-regulation of **attention**. One common practice involves continually directing attention to the unfolding of one's present-moment interoceptive or sensory experience (e.g., sensations of the breath), monitoring this attention, and bringing it back when it inevitably strays. Attention practices are thought to strengthen **meta-awareness**, the ability to observe and monitor one's internal processes of thinking and feeling [44**,45]. As a result, awareness is brought to bear on aspects of emotional experience that may otherwise go unnoticed, including bodily sensations, thoughts, and environmental stimuli, which may lead to improvements in emotion identification and regulation [46]. Training attention to one's present-moment experience has also been shown to reduce elaborative processing of stimuli [47] and to inhibit habitual behavioral responding (e.g., [48]). These changes may lead to more efficient and flexible uses of attentional resources, promoting more accurate and less catastrophic appraisals of one's present experience, as well as more adaptive behavioral responses to stressful events.

The deconstructive family refers to a set of self-inquiry techniques used to foster **insight** into processes of perception, emotion, and cognition. A common goal of such practices is to deconstruct maladaptive models of the self, others, and the world by interrogating the causes and conditions of one's present experience, and by observing the impermanence of phenomena (see [44**] for an illustration of this using the experience of anger as an example). One cognitive faculty targeted by deconstructive practices is **dereification** (also known as decentering or cognitive defusion), which occurs when thoughts, feelings, and perceptions are observed as temporary mental phenomena rather than accurate reflections of reality [44**–46]. Together,

dereification and meta-awareness may disrupt perseverative cognitions as well as the negative self-concepts and excessive self-referential processing implicated in depression and anxiety [44**,45,49,50]; they may also facilitate insights and reappraisals that support greater self-acceptance. Thoughts and events may also appear less threatening when understood as impermanent phenomena, and the ability to observe unpleasant experiences with greater granularity may similarly lessen their potency. These changes are likely to minimize experiential avoidance [46], which, in turn, may break the cycle of anticipatory anxiety, heightened reactivity, and prolonged recovery, in favor of more adaptive stress response profiles.

Finally, practices in the constructive family are intended to further cultivate psychological well-being by replacing maladaptive self-schemas with adaptive self-concepts [44**], and by developing prosocial qualities, such as kindness, compassion, empathetic joy and equanimity [51]. Psychological processes targeted by these practices include **perspective taking**, shifts in **appraisal**, and the generation of **positive affect** [44**,52], each of which may influence how acute stressors are perceived and responded to. These practices may be especially useful for managing acute stressors involving negative interactions with others. Indeed, initial evidence suggests that such practices alter acute responses to social-evaluative stressors. For instance, self-compassion training attenuated physiological and subjective stress reactivity to the Trier Social Stress Test (TSST) [53], and interventions involving dyadic meditation practices reduced cortisol reactivity to the TSST compared to attention-focused training [54].

Though each of these families of practice are likely to influence telomere regulation, the boundaries between them are not clear cut. Some practices are likely to target multiple psychological processes, and most meditation interventions combine several different practice types, making it difficult to distinguish their individual contributions. Additionally, individuals

will vary in how they interpret and implement these instructions [45], and the skills learned during formal meditation practice may manifest in a myriad of ways in daily life.

Meditation training contexts: safety and support

Meditation training may uniquely affect stress responding by promoting perceptions of safety—safety within the context of the self, in social exchanges, and by providing physically safe environments. Traditional stress-health models assume that stress degrades health through repeated activation of acute stress response systems (e.g. [55]). By contrast, the generalized unsafety theory of stress assumes that stress-response systems are predisposed to respond to threats, and are only inhibited by learned safety cues, including the presence of trusted individuals [56*]. This reconfigured model shifts the emphasis from acute stressors that activate stress responses, to the safety signals needed to dampen a threat-detection system that is ever at the ready [56*]. From this perspective, fundamentally altering explicit and implicit appraisal processes that modulate stress responding may require learning, or re-learning, safety cues until they become believed and habitual.

Meditation training often occurs in the context of a highly supportive environment. Residential retreats are the most extreme and unique example of this, where individuals are sequestered from real-world threats and demands, in a safe natural environment with their basic needs taken care of (see King et al., this issue [57]). This may be a particularly beneficial training format for individuals prone to maladaptive acute stress responses or with more ingrained telomere vulnerability factors, including experiences of early adversity, insecure attachments [58], and neuroticism (the latter indicated by our recent retreat study [8*]). Additionally, relationships with trusted teachers and a community of similarly motivated practitioners may

promote feelings of safety and activate schemas of secure attachment and interconnectedness.

These elements may play an important role in altering stress processes over and above the mental training aspects of meditation.

Conclusion

We have outlined several potential mechanisms through which meditation training may improve telomere biology via changes to habitual and acute stress processes (**Figure 1**). In articulating these pathways, this model may help to explain why a variety of meditation interventions, as well as other mind-body interventions, have been found to have positive effects on telomere biology as well as other stress-sensitive biological outcomes. As methods of measuring telomere biology become more reliable and available, the next generation of studies will be able to determine more definitively *if* meditation interventions impact telomere biology in a meaningful way. Understanding *how* these practices affect telomere biology will require a more systematic investigation of the various dimensions that make up meditation interventions, as well as better methods for capturing the phenomenological and psychological changes that might occur. Despite the complexity of these mind-body relationships, there is still a tremendous amount that can be learned about how meditation influences biological and cellular functioning.

Conflicts of interest

None of the four authors have any conflicts of interest to declare.

Acknowledgements

The preparation of this review was supported by the NIMH 5T32MH020006-20 “Consortium in Affective Science” predoctoral training grant (QC), an NIA R24AG048024 grant (EE, AC), an NIH K01AG057859 grant (AC) and funds from Hershey Family Foundation (CS). We gratefully acknowledge Brandon G. King for his thoughtful feedback on earlier drafts of the manuscript.

ACCEPTED MANUSCRIPT

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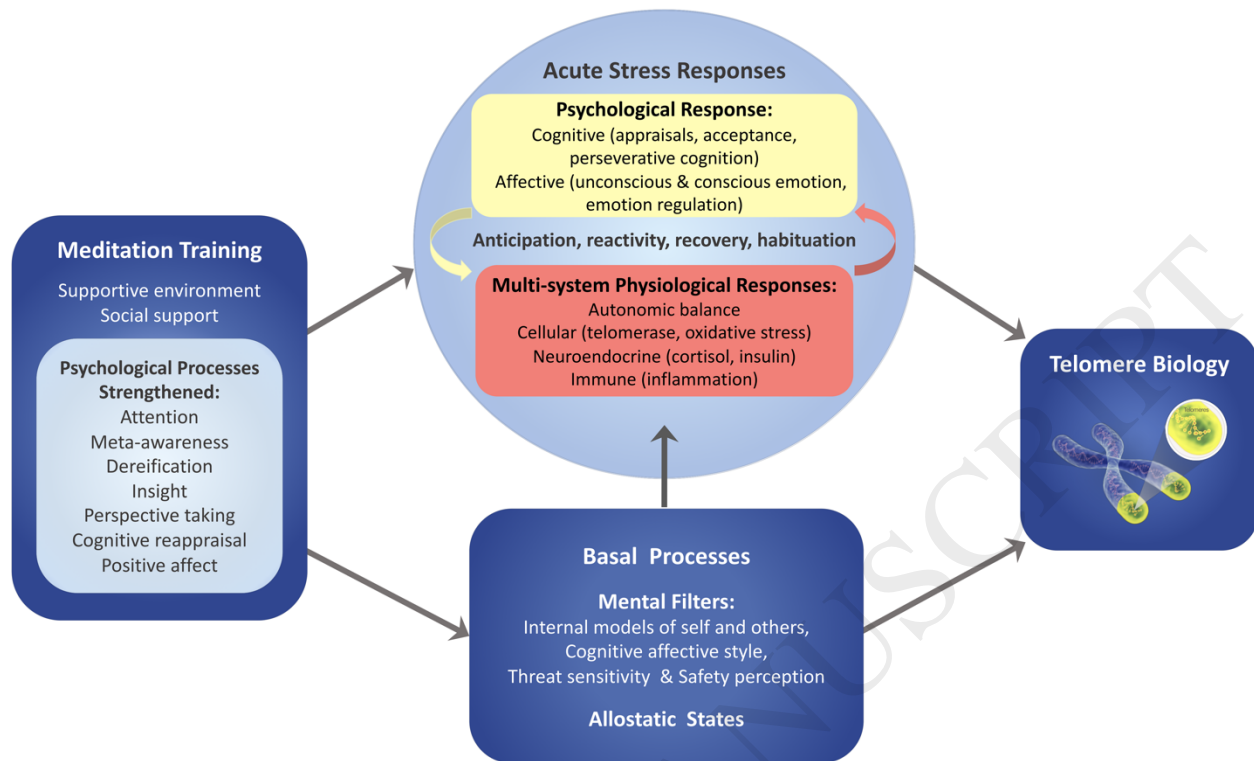


Figure 1: A theoretical model depicting how meditation training impacts telomere biology via stress processes (adapted from Figure 1 of Epel and Crosswell, et al. [28*]). Meditation training is expected to alter basal processes that influence acute stress responses, potentially resulting in fewer overall stress reactions. Training may also provide tools to reduce the severity of acute responses when they do occur. Only some of the mechanistic pathways proposed here have been tested. For example, there is evidence for the link between stress appraisals and telomere length [34] and for the ability of meditation training to enhance positive reappraisals (e.g., [59]), yet no intervention study has simultaneously assessed changes in stress appraisals and telomere biology to test this mediational pathway. With regard to perseverative cognitions, there is evidence that meditation training reduces rumination [60] and mind wandering [61], and that negative mind wandering is related to shorter telomeres [33], but no study has tested the association between telomere length and rumination. One small study of prostate cancer patients did, however, find that intervention-related increases in TA were associated with declines in individual's intrusive thoughts about their diagnosis [23]. While this study found that changes in avoidance were not related to increases in TA, another study found that telomere length was inversely related to experiential avoidance [7*]. Intervention-related increases in TA have also been linked to declines in morning cortisol [18], though no meditation intervention study has assessed acute reactivity in relation to telomere outcomes. Finally, there are multiple biological mechanisms that may result in TL changes, including increases in intracellular TA, alternative lengthening of telomeres, latent virus reactivation, and shifts in cell distributions [62]. These

biological mechanisms will need to be considered to map out a more complete model.

ACCEPTED MANUSCRIPT

Table 1: Meditation Interventions Measuring Telomere Outcomes

Study	Participant	Randomized	Control	Target Intervention	Target intervention length and intensity	Sample Size	Cell Type	Telomere-related	Assay method	Results
Jacobs et al. (2011)	Healthy experienced	Yes	Waitlist	Shamatha meditation retreat (<i>n</i>)	12 weeks: silent residential retreat including meditation ~ 6 h/d + vegetarian diet	Week 12	PB MC	Telomerase activity	TRAPeze kit	Greater TA in retreatants than controls post-retreat; TA was mediated by ↑
Daubenmier et al. (2012)	Overweight/obese	Yes	Waitlist	Mindfulness-based intervention	16 weeks: nine 2.5h group sessions + 1-day silent retreat	Baseline, post	PB MC	Telomerase activity	TRAPeze kit	↑ TA in both groups; changes in TA were negatively correlated with chronic stress, anxiety, dietary restraint, dietary fat intake,
Lavretsky et al. (2013)	Dementia caregivers	Yes	Listening to relaxation music (<i>n</i>)	Kirtan kriya (<i>n</i> =23)	8 weeks: cd-led meditation 12m/d	Baseline, post	PB MC	Telomerase activity	TRAPeze kit	↑ TA in meditators but not relaxation controls; ↑ TA was associated with ↑ quality of life in the meditators
Rao et al. (2015)	Healthy novices	—	None	Mind/body therapy	3 weeks: residential retreat including 1 h/d yoga & breath exercises	Baseline, week 3	PB MC	Telomerase activity	TRAPeze kit	↑ TA: 45% of people showed TA increases of
Kumar et al. (2015)	31-year-old obese man	—	None	Yoga-based lifestyle	10 days: active intervention with instructor 2 h/d, followed by 90-	Baseline, day 10, day 90	PB MC	Telomerase activity	Telomerase assay kit (Roche)	↑ TA
Epel et al. (2016)	Healthy experienced meditators & novices	Novice & vacation controls, yes;	Vacation controls (n=31) & novice meditators	Primordial sound meditation retreat (<i>n</i>)	4 days: residential retreat including meditation 3h/d + yoga 2h/d + lectures + interactive self-reflection exercises	Baseline, day 6, week 4, month 10	PB MC s	Telomerase activity & telomere-related	TRAPeze kit	↑ TA in experienced meditators (lower at baseline) but not novices or vacation controls
Ornish et al. (2008)	Low-risk prostate cancer	—	None	Comprehensive lifestyle intervention (<i>n</i>)	12 weeks: yoga & meditation 6h/w + moderate exercise 3 h/w + group support 1h/w + meetings with health staff 4 h/w	Baseline, week 12	PB MC s	Telomerase activity	TRAPeze kit	↑ TA associated with ↓ in LDL cholesterol and ↓ intrusive thoughts
Ornish et al. (2013)	Low-risk prostate	No	Active obser	Comprehensive lifestyle	Optional attendance of two 4h meetings/month following the	Baseline, year 4-5	PB MC	Telomerase activity &	TRAPeze kit (Millipore)	ns ↓ TA in both groups ↑ TL in treatment group compared to ↓ TL in
Conklin et al. (2018)	Healthy experienced	No	Life as usual	Insight meditation retreat (<i>n</i> =28)	4 weeks: ~ 9 h/d meditation during silent residential retreat + vegetarian diet	Baseline, week 3	PB MC s	Telomerase activity, telomere length, & telomere-	TRAPeze kit (Millipore); qRT-	No change in TA; ↑ TL in retreatants, which was moderated by levels of agreeableness and neuroticism; changes in gene expression supporting improved telomere maintenance
Lengacher et al. (2014)	Breast cancer patients	Yes	Treatment as usual	Variation of MBSR (<i>n</i>)	6 weeks: meditation & hatha yoga group sessions 2h/w + 15–45 m/d formal meditation + 15–	Baseline, week 6, week 12	PB MC	Telomerase activity & telomere-	TRAPeze kit (Chemicon); qRT-	↑ TA in MBSR participants (lower at baseline) compared to controls; No change in TL
Tolahunase et al. (2017)	Healthy participants	—	None	Yoga and meditation lifestyle	12 weeks: 120m sessions including yoga, meditation, & instruction 5 d/w	Baseline, week 12	PB MC	Telomerase activity & telomere-	Telomerase assay kit (Roche)	↑ TA; ns ↑ TL
Rima et al. (2016)	Fathers of retinoblastoma	—	Age-matched men w/ a healthy child	Yoga and meditation lifestyle	6 months: theory & practice sessions 2h/d	Baseline, week 12, month 6	Sp er	Telomere length	ELISA	TL ns shorter in fathers of children with RB than controls;
Wang et al. (2017)	Patients with depression, anxiety or stress &	Yes	Treatment as usual (mostly CBT; <i>n</i> =320)	Mindfulness-based group therapy (<i>n</i>)	8 weeks: mindfulness-based group therapy 2 h/w + meditation 20 m/d	Baseline, week 8	PB MC s	Telomere length	qRT-PCR	No change in TL
Thimmapuram et al. (2017)	Residents, faculty physicians &	No	Life as usual (<i>n</i> =12)	Heartfulness meditation (<i>n</i>)	12 weeks: meditation 20 m/morning + 5 m before bed + group	Baseline, week 12	Sal iva	Telomere length	Salivary kits (DNA, Genotek Inc. CA); qPCR	No change in TL overall; ↑ TL in meditators under 33 years old

Carlson et al. (2015)	Breast cancer	Yes	12-week supportive-expressive therapy	Mindfulness-based cancer recovery (MBCR; n=34)	8 weeks: group meetings 1.5h/w + 1 day silent retreat	MBSR: Baseline, week 8; SET: Baseline, week 12; Control: Baseline	Who	Telomere length	qPCR	TL was maintained in both intervention groups, but declined in controls
Duraimnai et al. (2015)	Hypertensive African	To parent study, but not this	Extensive health education	TM meditation + health education sessions (n=24)	16 weeks: 1.5-2hr meetings for first 6 days + 1h meetings follow-up twice/month + two 20m meditation sessions/d	Baseline, week 16	Sum	Telomere length & hTR/anhTERT	qRT-PCR	↑ hTR and hTERT mRNA expression in both groups; No change in TL
Bhasin et al. (2013)	Healthy novices	No	Experienced practitioners maintaining their own practice (n=26)	Relaxation Response (RR) training (n=26)	8 weeks: weekly individual training sessions from an experienced clinician + cd-led home practice 20m/day	Baseline, post: Samples were taken prior to, immediately after, and 15 minutes after listening to an	PBMCs	Telomere-related gene expression	Transcriptional profiling using Affymetrix human genome high throughput	Higher expression of telomere maintenance genes (i.e., HIST1H2BC, CACNA1C, and CYC1) in long-term practitioners than novices (before or after 8-week training) at baseline, which ↓ in response to the RR

Note: m=min; h=hour; d=day; w=week; ↑ = increases; ↓ = decreases; ns = not significant